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(71) Applicant *(for all designated States except US)*: CENTRAPHARM INC. [CA/CA]; Suite 3300, 100 Sherbrooke Street East, Montreal, Quebec H2X 1C3 (CA).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: KÉROUAC, René [CA/CA]; 295 de la Tournelle Road, Laval, Quebec H7G 1Z2 (CA). BRUTTMANN, Georges [FR/FR]; 2 Marcel Benoît Street, F–38000 Grenoble (FR).

(74) Agents: DUBUC, Jean, H. et al.; Goudreau Gage Dubuc & Martineau Walker, Stock Exchange Tower, Suite 3400, 800 Place–Victoria, P.O. Box 242, Montreal, Quebec H4Z 1E9 (CA).

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(54) Title: SUBLINGUAL DRUG FORMULATIONS HAVING COMBINED RAPID ONSET OF ACTION AND LONG LASTING THERAPEUTIC EFFECT

(57) Abstract

The invention relates to sublingual drug formulations containing active ingredients in dosages equal to or near standard oral dosages. A portion of sublingual form is sublingually absorbed and the remaining portion of the same is absorbed mainly by the enteral route. These formulations have a more rapid onset of action than and a termination of action similar to that of oral forms. As a result, the pharmacological effect is prolonged (almost doubled). Overall total bioavailability is the same as for oral forms. Formulations useful in the treatment of allergy and asthma are disclosed. They comprise at least one of the following: a β2–mimetic, a corticosteroid, an anti–H_1 histamine, an anti–cholinergic, a xanthine derivative, a non–steroid anti–inflammatory agent, an anti–leukotriene and a mast cell stabilizer.

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TITLE OF THE INVENTION

Sublingual drug formulations having combined rapid onset of action and long lasting therapeutic effect

FIELD OF THE INVENTION

This invention relates to sublingual drug formulations containing active ingredients in dosages equal to or near standard oral or enteral dosages.

BACKGROUND OF THE INVENTION

Administration of drugs through the mucosal lining of the mouth, either sublingually (from the area beneath the tongue which is rich in vascular and lymphatic vessels) or buccally (from the area between the cheek and the gum), has been known for many years. The advantages of the sublingual administration are the rapid absorption of drugs, a consequent rapid onset of action, and avoidance of extensive hepatic degradation. Despite these advantages, attention has focused during the recent years in increasing the duration of action, which focus translated in a great deal of references concerning the making of sustained-released formulations to be sublingually, buccally or orally absorbed. Sustained release of drugs is obtained by providing formulations comprising a polymer matrix which does not rapidly disintegrate, but rather keeps it integrity for a long time. Focus on sustained release preparation is indicative of a demand in the biomedical field for formulations of drugs which 1) do not require frequent administration, 2) do not provide episodes of maximal effect interspersed with episodes of lack of effect, and 3) avoid toxicity or undesirable side effects often accompanying the episode of maximal therapeutic peak effect. Although sustained release preparations may meet all these requirements, the above focus of research shows that long duration has been favoured at the expense of a quest for a rapid onset of action. Up to now, nobody has found a way to reconcile a rapid onset and long duration of action, and this without raising a toxicity problem. Sublingual administration pathway has been indeed reserved for a very few drugs.

Buccal and sublingual pellets comprising effective amounts of drugs are already known in the art.

USP 4,059,686 describes a sublingual or buccal formulation which has the property of adhering to the site of application due to the presence of sodium polyacrylate. As a consequence, the sublingual or buccal pellet slowly dissolves in mouth cavity. Although this reference states that the absorption of a medication is this way more efficient, it remains that the speed of absorption is presumably dependent on the speed of disintegration of the pellet. As a result, the medication is slowly released. This reference does not teach the absorption pharmacokinetics of the drugs, but it may inferred that a rapid absorption of drugs does not occur.

USP 4,226,848 also describes an adhesive buccal or sublingual formulation. A polysaccharide is added to an acrylate, causing adherence without irritation due to the acrylate component. Again, this reference does not teach a rapid release of medication. The release rate of a drug is clearly taught as being rather slow. A very general definition of what is meant by slow releasing is given in column 1, lines 26 to 31 of this patent. Further, the discussion related to Figure 1 of this patent, column 15, lines 33 to 51, clearly indicates that long lasting effect is sought and avoidance of a rapid absorption of a high amount of drug occurs, Figure 1 speaking by itself.

Quite recently, appeared on the market sublingual formulations of Isordil™ and of Ativan™. These formulations disintegrate very rapidly and release the drugs which are substantially absorbed by the sublingual route. Sublingual Ativan™exists in 0.5 - 4 mg dose units which are equivalent to the available oral forms. This drug is however particular because about the same doses appear to be absorbed notwithstanding the route of administration. Even an intravenous dose appears to be equivalent to what would be administered orally or sublingually. Plasmatic peak concentrations are also obtained at the same time without regard to the route of administration. This would mean that this drug is readily absorbed through the membranes and its bioavailability and pharmacokinetics are the same irrespective of the route of administration. There is no teachings of a sublingually formulated oral dose which would provide a sublingual absorption peak which precedes an "enteral-type" absorption peak (a second delayed peak due to absorption of drugs by another route) to minimize toxicity and to prolong the duration of effect.

Isordil™ is administered in a 5 - 10 mg sublingual dose while oral doses of 5 to 30 mg of the same drug are also available. It could be said that an oral dose of Isordil™ may be sublingually formulated. However, although the onset of action of the sublingual form is of two to five minutes and clearly precedes the onset of action of an oral formulation (30 minutes), the duration of action is much shorter for the sublingual form (one to two hours) than for the oral form (four to six hours). What is observed is a typical shift to the left of the total distribution without any second enteral-type absorption peak which prolongs the duration of action. It appears from these two examples of drugs commercially available that the nature of the drugs is such that the same amount of drugs is absorbed in a one step fashion, and the bioavailability is about the same, without regard to the route of administration. These two drugs are not deemed representative of the majority of drugs commercially available in oral forms.

The most renowned drug to be sublingually administered in rapidly disintegrating solid support is nitroglycerine. This drug has an oil/water partition coefficient higher than 1,800, the highest value being 2000. When sublingually formulated, the amount of nitroglycerine is known to be between 0.3 to 0.6 mg. Sublingual nitroglycerine has a very rapid onset of action and is used in emergency

situations or before an apprehended physical effort. The elimination of the drug is also rapid. The duration of action of nitroglycerine cannot be prolonged by administering a higher dose due to the toxicity thereof. It is clear that it would not be possible to administer a sublingual formulation of nitroglycerine comprising an orally effective dose thereof. When orally administered, ten times the amount necessary in the sublingual form of nitroglycerine is needed. If such a high amount of nitroglycerine was sublingually formulated, a too high amount of nitroglycerine which is a very lipophilic drug would be absorbed within a short time and would be toxic if not lethal.

Very few drugs have a high lipophilicity corresponding to the ideal model of nitroglycerin for sublingual absorption. Most of the drugs have an oil/water partition coefficient presumably between 40 and an undetermined value well below 2000. In this range, the sublingual absorption rate is proportional to the coefficient value and to the drug concentration gradient, because sublingual absorption is mostly governed by a phenomenon of passive diffusion through lipophilic membranes. Also, the solubility of a drug is another important factor to consider in the making of a drug formulation, because the concentration gradient may depend on this solubility.

Patents US 5,080,903 and 5,061,493 describe methods and compositions for sublingually administering β-2 mimetics and corticoids, respectively. These patents provide no teachings as to whether oral doses of medications may be formulated sublingually, and provide for rapid onset of action and long-lasting therapeutic effect.

Lipworth et al. (1989) in Eur. J. Clin. Pharmacol. 37(6): 567-571 [Abstract] disclose that sublingual administration of standard oral salbutamol tablets does not provide pharmacokinetics different from oral administration of the same. They conclude that "sublingual administration of salbutamol tablet has no clinical benefit over the oral route". It therefore appears that the oral tablet is not suitable for sublingual administration which requires a rapid disintegration for achieving an efficient sublingual absorption. So a sublingual specific and suitable vehicle appears determinant in the appearance of a sublingual absorption peak.

Ayache et al. (1990) in Biopharmaceutics & Drug Disposition 11: 279-309 disclose pharmacokinetic aspects of the sublingual administration of vincamine. Contrary to what would be expected, the sublingual solution and granule forms provide a retarded onset of action compared to the enteral form, because the sublingual forms are retained for a long time in the mouth. As a result, vincamine is overall absorbed in a higher amount in a sublingual form than in an oral form which is immediately swallowed. This reference does not teach a rapid onset of action combined to a long duration of action, with termination of action and area under the curve equivalent in both sublingual and enteral forms. Vincamine also appears to be a lipophilic and not very soluble drug which absorption depends on a gradient concentration which is not

built rapidly and in a highly enough sufficient amount to provide a good and rapid sublingual absorption.

None of the above patents teach that a combination of rapid absorption and long duration of action is possible with sublingual administration and this, without creating a problem of toxicity.

SUMMARY OF THE INVENTION

The present invention now provides a convenient way to formulate and administer medications which entail of a rapid onset and long duration of action, without creating toxicity.

This invention is mainly directed to sublingual formulations comprising drugs which do not have the same bioavailability and pharmacokinetics when a given dose is purely enterally or purely sublingually administered, so that a portion of the dose is sublingually and, optionally, absorbed during the disintegration time of the solid support while the remaining portion of the dose is enterally absorbed (that is what is meant by "enteral-type" absorption e.g. delayed absorption by another route than sublingual). The sublingual absorption peak preceding the enteral-type absorption peak, there is no cumulative toxic dose observed, a more rapid onset of action, the pharmacological action terminates at the same time and the duration of action is longer than that of a drug administered in an oral or enteral form.

It is therefore an object of the invention to provide a method of formulating and delivering a therapeutically effective amount of a medication, wherein the medication has a sublingual absorption pattern expressed in a plasmatic concentration of the medication over time, different from the enteral absorption pattern of the same medication, this method comprising a) formulating a rapidly disintegrating sublingual solid dosage form comprising an orally therapeutically effective amount of the medication; and b) sublingually administering the solid dosage form, wherein a portion of the medication is absorbed sublingually, giving rise to a first plasmatic peak of said medication, and wherein the remaining portion of the medication is orally absorbed giving rise to a second plasmatic peak delayed in time from the first plasmatic peak.

It is another object of the invention to provide a sublingual formulation for administering a medication to a patient, which comprises a solid support capable of a rapid disintegration under the action of saliva and a formulated orally effective dose of the medication, a portion of the formulated dose being sublingually absorbed as a pharmacologically active dose; whereby the sublingual formulation has a rapid onset of action due to the sublingually absorbed portion thereof and a termination of effect substantially the same as the termination of effect of an orally administered medication.

Under the scope of this invention are therefore drugs which do not have the same bioavailability and pharmacokinetics when a given dose is given purely orally and

purely sublingually, in such a way that a portion of the dose is sublingually absorbed during the disintegration time of the solid support while the remaining portion of the dose is substantially enterally absorbed. Furthermore, the sublingual absorption peak should precede the enteral-type absorption peak, in such a way that no cumulative toxic absorbed dose would be observed while the desired effect sought for is a rapid onset/long-lasting pharmacological effect.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS OF THE INVENTION

The drugs intended to be sublingually formulated in accordance with the present invention are already available in oral dosage forms. Preferably, drugs would have a potency such that they are pharmacologically active at an oral dose unit lower than about 30 - 50 mg. These drugs can enter the composition of a sublingual tablet made by direct compression or any other technique resulting in a rapidly disintegrating pellet, conveying to the creation of an optimal drug concentration gradient.

Such a sublingual formulation has the advantage of providing a rapid onset of action of a medication due to the proportion of the oral dose which is sublingually absorbed in a very short time (sublingual solid supports disintegrate almost instantaneously under the action of saliva, e.g. preferably within less than one minute, even more preferably, within 30 seconds). The remaining portion of the sublingually formulated medication may be buccally absorbed in part, and is swallowed and the pharmacokinetics of this remaining portion is substantially the same as when the whole formulated dose is orally administered. An oral dose of drug which is entirely converted into a sublingual dose of the same therefore combines a rapid onset of action and a long duration of action, the former being due to a sublingual (and/maybe buccal) absorption and the latter to a delayed enteral absorption. Since a determined portion of such an oral dose of medication formulated sublingually is absorbed very rapidly, this has for effect to achieve a rapid pharmacologically beneficial effect, without toxicity due to an uncontrolled and too high amount of sublingually absorbed medication. The absorption of the remaining portion of the formulated dose of medication is delayed, which has for effect to avoid coincidence of the sublingual and the enteral absorption peaks, resulting in an overall absorption of the medication which is not more toxic than the corresponding oral formulation of the same dose. To avoid toxicity, it is important that the portion sublingually absorbed be strictly controlled and that sublingual and enteral absorptions be non coincident to avoid cumulated absorption of a too high amount of medication. It is contemplated that an oral dose of a drug could be sublingually formulated if a proportion (maybe as little as about 1/100 to 1/2) is sublingually absorbed during the disintegration time of sublingual pellet. The absorbed remaining proportion would show a delayed pharmacokinetic pattern, typical of or

resembling an orally administered drug. Indeed, the enteral-type absorption would resemble the absorption of a second dose, e.g. a maintenance dose, without necessitating re-administering the medication.

A first overall advantage of this invention is that the total bioavailability of a sublingually formulated medication is almost equivalent to the bioavailability of a corresponding oral dosage form of the same. The main difference between oral dosage and sublingual dosage forms is the rapid onset of action due to the portion sublingually absorbed, which provides as a second advantage a prolonged duration of action.

This invention will be described by referring to the following examples and appended figure, which purpose is to illustrate this invention rather than to limit its scope.

BRIEF DESCRIPTION OF THE FIGURE

Figure 1 illustrates the blood concentration of salbutamol sulfate in subjects to whom was administered 8 mg of oral Ventolin™ (brand Salbutamol) versus the same quantity, namely 8 mg, sublingual salbutamol.

As illustrated in the following detailed description, the present invention demonstrates that an oral dose of drug can be sublingually formulated with a multiplicity of drugs. More specific experimental data is provided hereinbelow for salbutamol sulfate (a β-2 adrenergic mimetic used in the treatment of broncoconstriction), prednisolone (a corticosteroid used in the treatment of inflammation), and morphine hydrochloride or sulfate. Prednisolone precursor: prednisone, and derivative: methylprednisolone have also been tested (data not shown).

With the proviso that they will not have the same bioavailability and pharmacokinetics following purely sublingual and purely oral administration, further non-limitative examples of medications that may be advantageously formulated in sublingual forms are provided in Table 1.

TABLE 1

CATEGORY	EXAMPLES OF DRUGS	ORAL DOSES (MG)
Acne therapy	Isoretinoin	10 - 30
Anti-histaminic	Triprolidine	1.25 - 2.5
	Decarboethoxyloratadine	5 - 10
	Loratadine	5 - 10

CATEGORY	EXAMPLES OF DRUGS	ORAL DOSES (MG)
	Fexofenadine	60
	Norastemizole	10
	Terfenadine	60
	Diphenydramine	5 - 50
	Carbinoxamine	4 - 8
	Clemastine	1.3 - 2.7
	Tripelenamine	25 - 50
	Pynlamine	3 - 50
	Chlorpheniramine	1 - 12
	Dexchlorpheniramine	4 - 6
	Brompheniramine	4 - 12
	Promethazine	12.5 - 50
	Trimeprazine	2.5 - 5
	Methdilazine	4 - 8
	Cyproheptadine	4
	Azatadine	1
	Phenindamine	25
	Astemizole	10
	Cetirizine	5 - 10
Anti-H_2 histaminic	Farnotidine	20
Anti-migraine	Ergotamine	1
	Phenylpropanolamine	6.25 - 75
	S-fluoxetine	10 - 20
Decongestant	Pseudoephedrine	30 - 120
	Phenylpropanolamine	6.25 - 75
Anti-tussive	Dextromethorphan	2.5 - 30
	Codeine	10 - 60
	Hydromorphonone	1

CATEGORY	EXAMPLES OF DRUGS	ORAL DOSES (MG)
	Hydrocodone	1.6 - 5
	Caramiphen	10 - 40
	Carbetapentane	15 - 60
Anti-cholinergic	Hyoscyamine	.2 - .8
	Atropine	.04 - .16
	Biperiden	2
	Scopolamine	.01 - .04
	Benztropine	3
	Methscopolamine	2.5 - 5
	Ipratropium	4 - 12
	Oxybutinin	5
Diuretic	Furosemide	20 - 40
	Spironolactone	25
	Chlorthalidon	50
	Hydrochlorothiazide	25 - 50
	Amiloride	5
Anti-anginal/	Nadolol	40
Anti-hypertensive	Isosorbide	10 - 30
	Diltiazem	30
	Nifedipine	5 - 30
	Methyldopa	15 - 50
	Atenolol	50
	Clonidine	0.1 - 0.2
	Quinapril	5 - 30
	Perindopril	4
	Ramipril	1.25 - 10
	Captopril	6.25 - 30
	Enalapril	2.5 - 20

CATEGORY	EXAMPLES OF DRUGS	ORAL DOSES (MG)
	Indapamide	1.5 - 2.5
	Guanethidine	10 - 25
	Hydrolazine	10 - 50
	Metoprolol	50
	Prazocin	1 - 5
	Minoxidil	2.5 - 10
	S-doxazosin	1 - 4
	Trandolapril	0.5 - 2
Anti-convulsant	Nitrazepam	5 - 10
Antineoplastic	Melphalon	2
Anorexogenic	Fenfluramine	60
	Dexfenfluramine	15
Anxiolytic	Hydroxizide	10 - 50
	Chlorazepate	3.75 - 15
	Alprazolam	0.25
	Chlordiazepoxide	5 - 25
	Diazepam	2 - 10
	Flurazepam	15 - 30
	Lorazepam	0.5 - 2
Bronchodilator	Orciprenaline	10 - 20
	Ipratropium bromide*	4 - 12
	Theophylline	25 - 75
	Aminophylline	25 - 75
	Bambuterol	10
	Ephedrine	25 - 50
	Salbutamol	2 - 8
	R,R-formoterol	0.01

CATEGORY	EXAMPLES OF DRUGS	ORAL DOSES (MG)
	R-albuterol	0.6 - 1.3
	Terbutaline	2.5 - 5
	Metaproterenol	10 -20
	Salmeterol*	0.042 orally inhaled only
Vasopressor	Mitodrine	2.5 - 5
Antidepressant	Imipramine	10 - 50
	Amitryptiline	25
	Clomipramine	10 - 30
	Doxepin	10 - 30
Anti-diarrheal	Diphenoxylate/atropine	2.5/0.025
Androgen	Testosterone	30
Erectile dysfunction therapy	Yohimbine	2 - 6
Anti-coagulant	Nicoumalone	1 - 4
Anti-inflammatory	Flurbiprofen	30 - 50
	Diclophenac	25
	Indomethacin	25 - 50
	Ketoprofen	50
	S-Ketoprofen	50
	Tenoxicam	20
Muscle relaxant	Baclofen	10 - 20
Platelet inhibitor	Dipyridamole	25

CATEGORY	EXAMPLES OF DRUGS	ORAL DOSES (MG)
Prolactine inhibitor	Bromocryptine	2.5
Anti-emetic	Dimenhydrinate	10 - 50
	Metoclopramide	5 -10
	R-Ondansetron	4 - 8
Anti-psychotic	Fluphenazine	1 - 5
	Haloperidol	0.5 - 10
	Loxapine	5 - 25
Hypoglycemiant	Glyburide	2.5 - 5
	Glicazide	80
Antibiotic	Minocycline	50
	Nitrofurantoin	50
	2R,4S-Itraconazole	100
Steroid	Prednisone/Prednisolone	4 - 15
	Methylprednisolone	5 - 15
Analgesic	Morphine	5 - 20
	R-Ketoprofen	50
	R-Ketorolac	10
	Hydromorphonone	2 - 4
	Codeine	3 - 10
Expectorant	Guafenesin	33 - 100
	Guaicolsulfate	45
	Terpin	80
	Ammonium chloride	33 - 80
	Glycerol guaicolate	30
	Iodinated glycerol	30 - 60

CATEGORY	EXAMPLES OF DRUGS	ORAL DOSES (MG)
Leukotriene Antagonist	Zafirlukast	20
	Montelukast	5 - 10
Anti-ulcer	Norcisapride	5 - 20
Mast cell stabilizer	Disodium cromoglycate	100
Anti-incontinence	S-oxybutynin	5

* oral spray doses.

Oral doses of drugs were given to a small panel of normal subjects and, after a recovery period, the same doses, this time sublingually formulated, or the converse (sublingual first and oral second) were administered. Surprisingly, it has been observed that the sublingual formulations of the present invention display overall total bioavailability similar to enteral formulations of the same medications. However, a rapid onset of action occurred solely with the sublingual forms. This more rapid onset provides a longer duration of action when compared to that of the oral formulation. When formulated and administered sublingually, the drugs showed pharmacokinetics clearly different and clearly advantageous in comparison with the pharmacokinetics of the same drug administered orally.

In accordance with the sublingual formulations of the present invention, a first plasmatic peak was observed, which peak precedes by thirty to sixty minutes the peak normally produced by orally administered drugs. Further, following sublingual administration, a second delayed peak which apparently corresponds in time and magnitude to an enteral-type absorption peak of the non-sublingually absorbed portion of the drug followed the sublingual absorption peak. After the first and second peaks are obtained, the blood circulating levels of medications slowly decrease during a drug elimination phase, as is the case of orally administered medication.

Advantageously, the overall effect of the sublingual formulations of the present invention is a "hybrid" rapid onset/long-lasting effect. A further advantage is that the sublingual formulations of the present invention minimize the risk of administering toxic doses of a drug since the sublingual and enteral absorption peaks do not coincide in time.

The main factors which govern a drug dosage regimen are:

- **drug bioavailability**
- **drug potency**
- **drug toxicity**; and
- **drug elimination**

Drug bioavailability:

This factor defines a proportion of an administered drug that is absorbed and available for pharmacological activity, which proportion is expressed as a percentage of the drug available when intravenously administered. In an oral or enteral form, this factor depends on how much intact drug crosses the gastrointestinal membranes. If, for most drugs, absorption is achieved by passive diffusion, the same physical principles should govern the sublingual as well as the enteral absorption. Passive diffusion of a drug depends on the combination of two phenomena: the lipophilic character of the drug and its gradient of concentration. During enteral absorption, a drug can be subject to more or less extensive degradation, binding to and/or dilution in gastrointestinal content, and to various ionisation states due to pH variations. A plasmatic peak can take time to build because the drug is rather slowly absorbed and a proportion thereof is eliminated at the same time. Moreover, a certain amount of drug can never be absorbed. In the present invention, the overall bioavailability of the sublingual drug is the same as for the oral drug, but follows a two-step pattern. The sublingual absorption makes a small but nevertheless pharmacologically active portion of the dose to be rapidly available and the enteral-type absorption makes the remaining portion to be as available as the oral dose of the same drug.

Moreover, the lipophilicity of some drugs which are weak acids and bases may be modified to a certain extent by increasing or diminishing the formulation pH, which has for effect to decrease or increase the net charge of the drug which becomes more or less lipophilic and permeant. The two parameters of an optimal passive diffusion can therefore be adjusted to achieve a sublingual formulation which would make a controlled amount of drug to be sublingually absorbed.

Once that amount obtained, the remaining portion of the dose that is presumably swallowed does not provide more toxicity than for a corresponding typical oral dose, and provides sort of a maintenance dose and long duration of effect.

Drug potency:

Potency is determined simply by the dose needed to obtain a particular effect of a given intensity.

This factor depends on the affinity of the drug for its receptor. Usually, a reference value for drug potency is represented by an effective amount of intravenously administered drug (where the bioavailability is 100%). The concentration of plasmatic drug is usually obtained very shortly after intravenous administration, prior to any substantive elimination. The ratio Amount of administered drug/Plasmatic concentration provides a value for the apparent volume of distribution. A drug is called potent if the plasmatic concentration needed for a given pharmacological effect is low.

Drug toxicity (side effects):

This factor depends of the safety margin of a drug and individual susceptibility thereto. When calculating a dosage unit, drug doses are formulated in function of practical dosage intervals. This means that higher than necessary doses can be formulated to obtain a maximal effect during the longest time possible. For example, if the half-time of a medication is about 7 hours, one has a choice to formulate a dose of medication given at 6 hour intervals or to formulate a higher dose of medication given more conveniently at 8 hour intervals. The choice will be guided by the safety margin of the medication, and the probability that the patients experience undesirable side effects. In the present invention, the administration interval of the sublingual formulations is the same as for the selected commonly used oral doses, because the pharmacological action of sublingual forms terminates at the same time as for a corresponding oral dose. Further, the toxicity of the sublingual formulations of the invention will not be increased with regard to the toxicity occurring with the corresponding oral doses, in so far as the sublingual absorption does not provide a toxic plasmatic peak and in so far as the sublingual and enteral-type absorption peaks do not coincide to reach toxic values. Because the sublingually absorbed portion of the sublingual dose is strictly controlled, and because the sublingual absorption peak does not coincide with the enteral absorption peak, the risk of higher toxicity for a sublingual dosage form is minimized.

Drug elimination:

This factor depends on the capacity of the recipient organism to remove the active drug from blood and tissues. The drug can be metabolized and/or cleared from the body. This factor is independent of the route of administration except if a drug is subject to extensive presystemic degradation. In fact, drugs can be subject to degradation by gastrointestinal environment (enzymes,

bacteria, etc.) or to extensive degradation during their very first passage through the liver. In these cases, a sublingual dose will have a much better chance than the same oral dose to distribute throughout the whole body before being inactivated. The highest the first hepatic passage effect is for an orally administered drug, the lowest is the proportion of an oral dose of drug which should be sublingually absorbed for achieving a pharmacological effect. Once the plasmatic peaks are obtained, both sublingual and oral forms of drugs show the same kinetics of elimination. Normally, one would expect that the sublingually absorbed drugs would terminate their action more rapidly, e.g. the whole distribution curve should shift to the left (like such is the case for Isordil™).

However, the portion of the drug that is not sublingually absorbed constitutes an enteral-type dose. This portion provides a second delayed plasmatic peak of absorption which maintains the blood concentration of drug levels at active levels during at least the same time as for a dose of drug totally administered in the oral form. Therefore, the second peak of a sublingually formulated oral dose acts like a maintenance dose without necessitating re-administration of the drug.

Moreover, since the sublingual and enteral absorption peaks do not coincide, the risk of administering a toxic dose is minimized. In the cases tested, it was observed that the enteral-type absorption of sublingually administered drugs starts to build a plasmatic peak when the sublingual absorption peak starts to decline (e.g. elimination phase in undergoing for the sublingually absorbed dose, but is masked or truncated by the incoming enteral-type absorption peak).

Example 1: Sublingual Salbutamol sulfate

Sublingual salbutamol sulfate have been made using a technique of direct compression as described in published French patent publication 2,640,138. Briefly, one weight of microgranulated lactose (W_1) is admixed to an equal weight ($W_{1'}$) of lyophilized or powdered salbutamol sulfate. Twice the weight ($2 \times W_1$) of microgranulated lactose is further homogenised with the mixture ($W_1 + W_{1'}$). This operation is repeated until a mixture weight of lactose/salbutamol equals about 70 - 85% of the desired total weight, while keeping the lactose component in a proportion higher than about 50%. This means that, generally, a pellet of 100 mg would contain a maximum of about 30 mg of drug. Microcrystalline cellulose (about 12.5 mg) and sodium croscarmellose (about 2.5 mg) are added to the last mixture and homogenisation is allowed to proceed for 30 minutes. A wetting agent such as magnesium stearate (about 0.5 mg) is added and homogenisation further proceeds for 5 minutes to obtain a final desired mixture. The mixture is then distributed in casting molds (a lower compartment divided in pellet compartments of a desired weight), and

compressed with the aid of a upper punch under a controlled pressure to avoid high compaction of the components of the sublingual pellets, which would impede with rapid disintegration. Usually a pressure of less than about 5 kg is suitable for obtaining a sublingual pellet capable of disintegrating within 2 minutes under the tongue.

It is worthwhile noting that the formulations of the present invention are not limited to ones comprising the above excipients. For example, sodium croscarmellose has been tried up to at least 4 mg with an excellent short disintegration time. Sodium croscarmellose has also been replaced by the same amount (4 mg) of sodium starch glycolate, with equivalent or even better results. Also, different forms of lactose provide for different disintegration times. Indeed, the form of the lactose appeared to be more determinant for the disintegration time than the other excipients. Good examples of excipients are lactose DCL-21 (83 mg), cellulose microcrystalline (Avicel ™, 12.5 mg), sodium starch glycolate (Explotab™, 4mg) or sodium croscarmellose (Ac-Di-Sol™ 4mg), and magnesium stearate (0.5 mg). Suitable hardness of the pellets was obtained at about 3 kPa and the disintegration time of the two latter excipients was about 30 seconds or less.

Sublingual salbutamol has been formulated to comprise usually prescribed oral doses thereof: 2, 4, and 8 mg. For the purpose of measuring detectable plasma levels of salbutamol, higher doses of 6 and 8 mg have been particularly tested.

Sublingual doses of 4, 6 or 8 mg salbutamol were given to a small panel of normal subjects and the pharmacokinetics have been compared to the same oral doses of salbutamol (Ventolin™) in the same patients. Salbutamol has been measured in plasma at times indicated in Table 2, using a detection technique based on the one described by Weisberger et al. (Biol. Mass Spectr. 10: 15-17 (1983)). Comparative results are presented in Table 2 and Figure 1, wherein one can appreciate that, after 60 minutes, a first sublingual absorption peak in obtained at a plasma concentration equivalent to the amount observed 150 minutes after oral administration of Ventolin™. In both cases, an enteral-like absorption peak of about the same magnitude is observed at 180 minutes, which would mean that a presumably swallowed proportion of sublingual salbutamol repletes a plasma pool of salbutamol at a time where the sublingual absorption peak begins to decay (elimination phase). The areas under the curves are not statistically different, and the termination of action occurs at the same time. It is reported that Ventolin™ has an onset of action of about 30 minutes. Unfortunately, at this time, for doses of 2 - 4 mg, the plasmatic concentration is very close to and even under the limit of detection of the technique (1-2 ng). At the highest dose tested (8 mg), Ventolin™ showed a concentration of about 3 ± 1.5 ng/mL after 30 minutes, which may confirm that, after 30 minutes, a dose of 4 mg would have shown a value close to 1 - 1.5 ng/mL. One could assume that the onset of action of the sublingual form at the usual 4 mg dose is very close to 15 minutes; most importantly

the maximal effect is achieved within one hour instead of 3 hours (e.g. it is assumed that a dose of 2 - 4 mg follows the same kinetics as for higher doses of 6 and 8 mg). Overall, the sublingual effect lasts from the 1st to at least the 4th hours, which is clearly more expanded (doubled) than for the corresponding oral form (from the 2.5th to the 4th hour).

TABLE 2: Comparison between average plasmatic levels of salbutamol sulfate obtained after oral administration (Ventolin™) and sublingual administration thereof.

Time (hours)	Oral Form Ventolin* Tablet (ng/ml)	Sublingual Form Salbutamol* (ng/ml)
T0	0	0
15 min	0.34±0.29	1.22±1.19
30 min	2.79±1.68	5.35±5.78
1H	5.44±2.24	8.44±8.55
1H30	6.10±2.74	7.36±3.75
2H	6.77±2.98	8.14±2.46
2H30	8.32±2.50	8.62±2.50
3H	13.07±6.55	11.84±7.35
4H	10.44±3.44	8.92±1.88
6H	6.80±2.00	6.03±1.56
8H	5.06±1.47	5.06±1.32
10H	4.05±1.31	3.73±0.73
12H	3.30±1.14	2.83±1.05
16H	2.09±0.81	2.05±0.99
24H	1.24±0.50	1.43±0.30
36H	0.51±0.47	0.30±0.26

Example 2: Sublingual prednisolone

A sublingual prednisolone formulation comprising a unit dose of 15 mg has been made using the same procedure as described in Example 1. Comparative studies with oral prednisolone have also been conducted and the same profiles as for salbutamol have been obtained. A sublingual peak was observed at 1 hour followed by an enteral peak at 2 - 2.5 hours. The effect lasts from 1 h - 4 h after administration.

Example 3: Analgesic compositions

As an exemplary composition of this category, sublingual pellets comprising oral doses of morphine (5 - 20 mg), hydromorphonone (2 - 4 mg) or codeine (3 - 8 mg) can also be made. Morphine 10 and 20 mg (sulfate and hydrochloride forms) have shown a double-peak effect similar to the one observed in Examples 1 and 2, when administered as sublingual liquids. The double-peak effect would be even more accentuated for a sublingual solid dosage form which creates a greater concentration gradient.

Example 4: Anti-asthma and anti-allergy drugs

Since a field of interest of the present inventions relates to the treatment of respiratory diseases such as asthma and allergy, diverse combinations of suitable drugs are contemplated. The β_2 mimetic being the actual drug of choice for relieving bronchoconstriction, the preferred therapeutic approaches comprise treating with a β-2 mimetic and at least one of the other drugs mentioned in Table 1 or other drugs, active against bronchoconstriction. One can even combine long and short-active drugs. As drugs complementary to β_2 mimetics, the following classes thereof are contemplated: corticosteroids, anti-histamines, anti-cholinergics, xanthine derivatives, non-steroid anti-inflammatory agents, anti-leukotrienes, decongestants, expectorants, anti-tussives, and mast cell stabilizers. A sublingual formulation for treating respiratory diseases such as allergy and asthma should therefore comprise at least salbutamol or at least one drug from the above complementary classes. It may also comprise salbutamol and at least one drug selected from the above complementary classes.

Salbutamol sulfate (oral doses of 2 - 4 mg) or isomer thereof is one example of a β_2-mimetic, while prednisolone or its methylated derivative (4 - 15 mg) or its precursor prednisone (15 mg) are examples of corticosteroids. As a xanthine derivative, theophylline or aminophylline (25 mg) is particularly considered. As another β-mimetic, orciprenaline (10-20 mg) is also particularly considered. As a H_1-anti-histamine, loratadine (5-10 mg), its metabolite decarboethoxyloratadine, terfenadine (60 mg), or its metabolite fexofenadine are also considered as examples. As an anticholinergic, ipratropuim bromide (oral dose pharmacologically equivalent to an oral spray dose of 4 - 12 mg) is particularly considered. As another anti-inflammatory agent, a bradykinin receptor antagonist (B_1 or B_1/B_2) is contemplated as well as any non steroid anti-inflammatory agent. Anti-leukotrienes such as zafirlukast and montelukast are also particularly considered. Decongestants, expectorants, anti-tussives and mast cell stabilizers may also complement any of the aforementioned drugs to alleviate undesirable symptoms or to complement pharmacological efficacy.

Example 5: Anti-allergy regimen therapy

Such a regimen includes desensitization, specific and non-specific, in accordance with the sublingual method and compositions described in CA 1,329,544, US 5,244,663 and CA 1,328,600. For relieving allergy crisis, any of suitable compositions selected within those of Example 4 are to be administered. Desensitization may be concurrent with alleviation of allergic symptoms. Kits comprising allergens and medications for alleviating allergy symptoms are also contemplated.

Example 6: Anti-hypertensive drugs

As exemplary compositions of this category, sublingual compositions comprising oral doses of enalaprilat (oral doses of 2.5 - 20 mg) and/or hydrochlorothiazide (25 - 30 mg) can be made using the procedure of Example 1. Further, compositions comprising prazocin (1 - 5 mg), or minoxidil (2.5 - 10 mg) can also be made as well as any other composition of this category comprising a suitable oral dose of at least one drug of interest.

Example 7: Anti-migraine drugs

As exemplary compositions of this category, compositions comprising oral doses of ergotamine tartrate (1 mg) can also be made.

Metoclopramide (5 - 10 mg) or dimenhydrinate (10 - 30 mg) may also be added to treat an emetic effect of an ergot alkaloid.

Example 8: Anti-emetic drugs

As exemplary compositions of this category, compositions comprising oral doses of metoclopramide (5 - 10 mg) or dimenhydrinate (10 - 30 mg) can also be made, using the same procedure as in Example 1.

Example 9: Erectile dysfunction therapy

As an exemplary composition of this category, yohimbine (oral dose of about 2 - 6 mg) can also be formulated sublingually, again using the above procedure.

Example 10: NSAID's

As an exemplary composition of this category, indomethacin (25 mg) or tenoxicam (20 mg) can also be sublingually formulated using the procedure of Example 1.

Example 11: Anticoagulants

As an exemplary composition of this category, nicoumalone (1 - 4 mg) can also be sublingually formulated using the procedure of Example 1.

Example 12: Anticonvulsants

As an exemplary composition of this category, nitrazepam (5 - 10 mg) can also be sublingually formulated using the procedure of Example 1.

Example 13: Antidepressants

As an exemplary composition of this category, clomipramine (10 - 25 mg) can also be sublingually formulated using the procedure of Example 1.

Example 14: Antidiarrheals

As an exemplary composition of this category, diphenoxylate (2.5 mg) and atropine sulfate (0.025mg) can also be sublingually formulated using the procedure of Example 1.

Example 15: Antipsychotics

As an exemplary composition of this category, loxapine (5 - 25 mg) can also be sublingually formulated using the procedure of Example 1.

Example 16: Antispamodics

As an exemplary composition of this category, baclofen (10 - 20 mg) can also be sublingually formulated using the procedure of Example 1.

Example 17: Adjuvant and complementary therapies

Any adjuvant medication capable of alleviating undesirable side effects of a medication may enter the above formulations as such is the case for an anti-emetic combined to ergotamine (See Example 7). Complementary therapies are exemplified in Example 4 for allergy or asthma treatment. An other exemplary class of disease which would benefit from complementary therapy is hypertension. The limiting amount of drugs to combine is governed by the maximal drug capacity of the sublingual pellet.

Example 18: Drug interactions

Drug interactions are documented in the art. Oral doses of drugs can therefore be increased or decreased, depending on other drugs separately administered to patients or inherently combined in the sublingual formulations.

Example 19: Pediatric compositions

Frequently, indicated oral doses prescribed for adults are divided by a factor of 2 for children under 12, and by a factor of 4 four children under 4 years old, respectively. Therefore, in all the above Examples, corresponding ½ and ¼ doses are made to treat young patients, if indicated. Further, many drugs which oral dosage is too high to be converted into a sublingual formulation may become suitable when the latter is intended for children, because of the required division factor of 2 or 4.

Example 20: Manipulation of lipophilicity

Absorption of drugs may be modified by adding enhancers such as non-ionic detergents (ex.: Tweens™), which modify the fluidity of the membranes. Besides that, the formulation pH may also be modified to optimize the electronic charge of the drug (less charged drugs are more lipophilic and more absorbed, and vice-versa).

Example 21: Other additives

Sublingual formulations may comprise additives such as flavours and/or sweetening agents, which confer a pleasant and more acceptable taste to the patient or which avoids too much salivation. Corticosteroids, for example, have a bitter taste. Pellets of a final weight of 135 mg comprising 4 mg of methylprednisolone, 90 mg lactose, 12.5 mg cellulose, 2.5 mg croscarmellose, 1 mg magnesium stearate, 5 mg sodium saccharinate, 5 mg vanilla aroma extract and 15 mg orange aroma extract, have been made and have been well accepted.

Example 22: Equivalents and Others

It will appear obvious, upon reading the disclosure, that another solid support than the specific ones detailed can be made. The leading criterion to meet is a rapid disintegration time allowing rapid therapeutic onset through optimal sublingual absorption followed by gradual enteral absorption. Other techniques than direct compression may be used to make the final form of a sublingual pellet. For example, impregnation of the solid support with solutions comprising controlled amounts of drugs can be equally used. Even granules are contemplated, which would permit splitting doses accurately when used in combination with a granule distributor flask, especially for drugs which have a low safety margin. Any drug defined hereinabove may have derivatives, precursors (pro-drugs), active metabolites and/or equivalents (the term "equivalent" defining any other drug of the same class which is equivalently active, without being necessarily equipotent or as selective for a given type of receptor). All these precursors, metabolites, derivatives and equivalents are within the scope of this invention provided that they show the same properties when sublingually administered: rapid onset of action and long-lasting effect. Also, the above drugs are cited as examples for each category of exemplified medications. Any other drug acting on the same tissue target or even on different targets and which end point effect is the same as represented in the name of the category is within the scope of the invention. Finally other categories of drugs may be sublingually formulated, using direct compression, impregnation or other techniques. The list of drugs of Table 1 and Examples 1 to 16 is therefore not exhaustive and many others will benefit from a sublingual route of administration. All drugs as taught by the present invention which do not provide the same pharmacokinetics and bioavailability when purely sublingually and purely enterally absorbed are within the scope of this invention. Finally, if drugs which do not have the same oral interval of dosage are mixed in the same formulations, the doses

may be adjusted to take into account the interval of sublingual dosage (longer or shorter) to avoid toxicity while preserving efficacy.

Although the invention has been described above with respect with one specific form, it will be evident to the person skilled in the art that it may be modified and refined in various ways. It is therefore wished to have it understood that the present invention should not be limited in scope, except by the terms of the appended claims.

What is claimed is:

1. A method of formulating a therapeutically effective amount of a medication in a sublingual form, wherein said medication has a sublingual absorption pattern expressed in plasmatic concentration of the medication over time different from the enteral absorption pattern of the same medication, said method comprising formulating a rapidly disintegrating sublingual solid dosage form comprising an oral therapeutically effective amount of said medication; whereby, when said sublingual solid dosage form is administered to a patient, a portion of said medication is absorbed sublingually, giving rise to a first plasmatic peak of said medication, and the remaining portion of said medication is orally absorbed, giving rise to a second plasmatic peak delayed in time from the first plasmatic peak; whereby said medication has a rapid onset of action due to the sublingually absorbed portion thereof and a termination of effect substantially coincident with that of an orally administered medication.

2. A sublingual formulation for administering a medication to a patient, which comprises a solid support capable of a rapid disintegration under the action of saliva and a formulated orally effective dose of said medication, a portion of said formulated dose being sublingually absorbed as a pharmacologically active dose; whereby said sublingual formulation has a rapid onset of action due to the sublingually absorbed portion thereof and a termination of effect substantially coincident with that of an orally administered medication.

3. A sublingual formulation as defined in claim 2, wherein said solid support comprises pulverulent lactose as an excipient.

4. A sublingual formulation as defined in claim 3, wherein said pulverulent lactose is in a proportion of about 50-85 weight %.

5. A sublingual formulation as defined in claim 4, wherein said pulverulent lactose is in a proportion of at least about 70 weight %.

6. A sublingual formulation as defined in claim 5, wherein said pulverulent lactose is lactose DCL-21.

7. A sublingual formulation as defined in any one of claims 3 to 6, wherein said solid support further comprises microcrystalline cellulose, sodium croscarmellose or sodium starch glycolate, and magnesium stearate.

8. A sublingual formulation as defined in any one of claims 2 to 7, wherein said formulated orally effective dose of said medication present in a proportion not exceeding about 30% of a final weight of said formulation.

9. A sublingual formulation as defined in any one of claims to 2 to 8, which is made by direct compression.

10. A sublingual formulation as defined in any one of claims 2 to 9, wherein said medication is salbutamol sulfate, prednisolone, methylprednisolone, prednisone, morphine sulfate or morphine chloride.

11. A sublingual formulation as defined in any one of claims 2 to 9, wherein said medication comprises a drug selected from the group consisting of a β2-mimetic, a corticosteroid, an anti-H_1 histamine, an anti-cholinergic, a xanthine derivative, a non-steroid anti-inflammatory agent, an anti-leukotriene, a mast cell stabilizer and any mixture thereof.

12. A sublingual formulation as defined in claim 11, wherein said medication comprises a β2-mimetic.

13. A sublingual formulation as defined in claim 12, wherein said β2-mimetic is salbutamol sulfate.

14. A sublingual formulation as defined in claim 12 or 13, wherein said medication further comprises at least one other drug of said group which is effective in relieving bronchoconstriction.

15. The use of a sublingual formulation as defined in any one of claims 11 to 14 for the treatment of asthma.

16. The use of a sublingual formulation as defined in any one of claims 11 to 14 for the treatment of allergy.

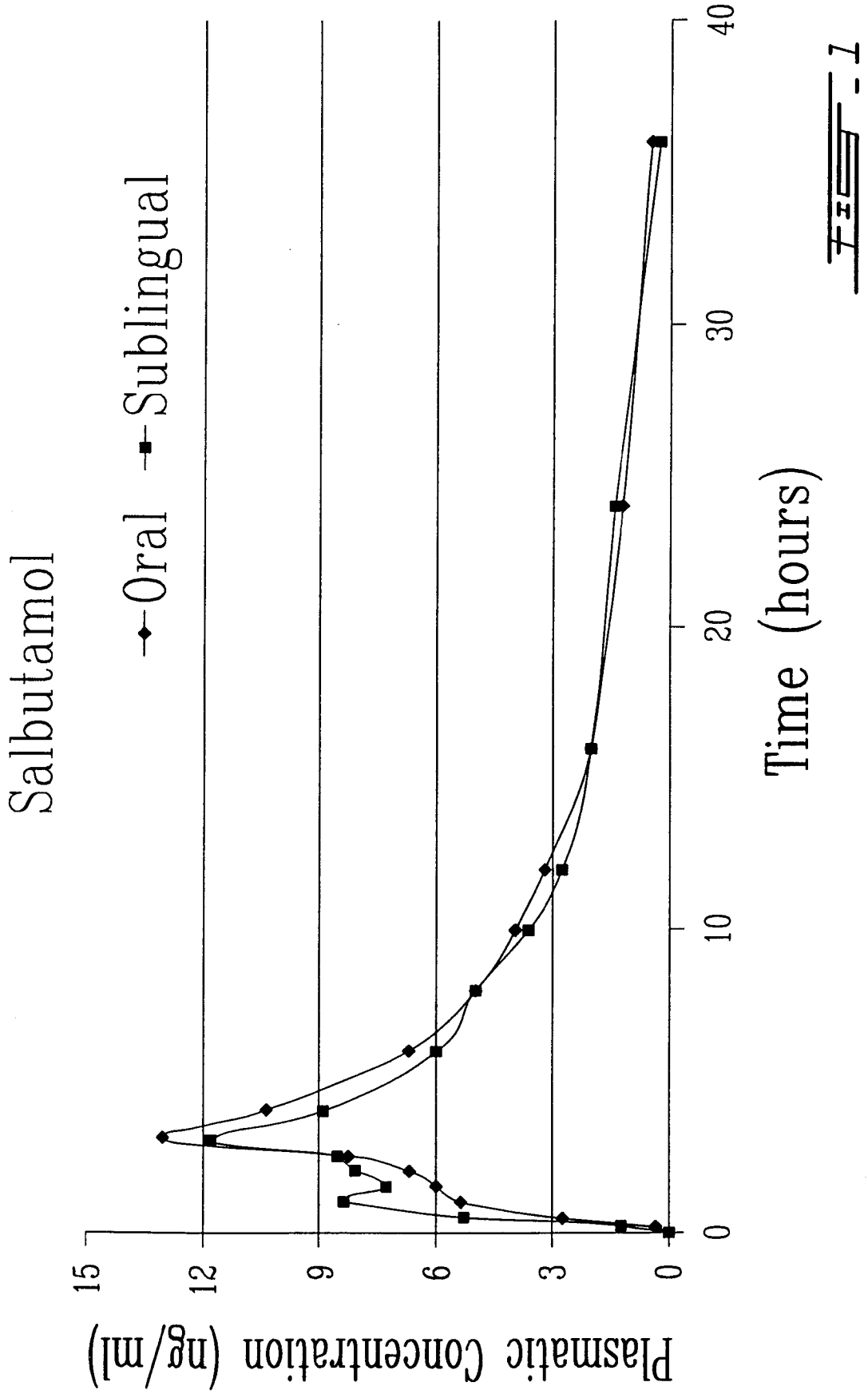
Salbutamol
Oral
Sublingual
Plasmatic Concentration (ng/ml)
15
12
9
6
3
0
0
10
20
30
40
Time (hours)

Fig - 1